# New Synthetic Approach for Manufacturing of Iron Salt and Calcium Salt

SUMMARY FOR THE DEGREE OF

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## 1. Introduction

Globally pharmaceutical industries are striving to achieve low-cost and high-quality products with a forward-looking approach to ensure long-term success and a continual improvement process [1], [2]. India ranks 3rd by volume in pharmaceutical production. This makes it crucial for Small and Medium sized Enterprises (SMEs) of the Indian Pharmaceutical Industry to sustain global quality standards with retrieving business challenges in the current situation.

Taking note of this new manufacturing reality, regulators like USFDA, are also envisioning to shift towards an agile, efficient, pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight [3]. The unison of the forward-looking manufacturing and regulatory trends bode well for supporting a wider implementation of continual improvement systems which in turn also support sustained growth for the companies [4]. Some of the initial steps in this direction (e.g. ICH Q8, 9, 10, and 11 guidelines) acknowledge the paradigm shift from product to process knowledge and have proven to be helpful to industries [5].

Amongst the approaches for achieving continual improvements, operational excellence is emerging as a popular option. With its Japanese roots, the operational excellence framework has been well established in the automobiles industries, however, the adoption in pharmaceutical industries is in early stages. Operational excellence can be viewed as the state of a business organization accomplished through the continuous innovation and technology implementation in the products and services it offers [6]. In the course of achieving this state of operational excellence, organizations are bound to pursue/achieve continual improvements and sustainable growth [7]. To achieve operational excellence various enablers are applied by the organization. These enablers are tools that help the organization continually improve. Total Quality Management (TQM), Lean, Six Sigma, Kaizen, and Industry 4.0 are a few examples.

The diversity of manufacturing types coupled with the varying scale of operation (small to large scale industries) challenges the implementation of generalized guidelines for implementing operational excellence. In particular, micro, small and medium (MSME) scale industries, which contribute up to 40% of production [8], may face an additional hurdle of achieving operational excellence due to technical constraints of the workforce and limited investment capacity. All together this situation warrants an urgent need for improving the understanding of approaches to

implement an operational excellence program that is tailored to the need of each organization.

### 1.1. Impact and challenges of implementing operational excellence

Operational excellence had a positive impact of majorly five key elements of a pharmaceutical manufacturing industry: (i) variation in production, (ii) rejection rates, (iii) resource utilization, (iv) process improvement, and (v) achieving compliance. It reduced variation in production and hence less of reprocess and reworks. It also reduced rejection rates which aided in good quality products. It increased the utilization of resources to its maximum limit proving the operational excellence from business perspective. With operational excellence came a cultural change in all the people of the organisation and hence, there is an approach of continual improvements for all the processes. All these together brought the shift towards investigative, root cause analysis approach leading to continual improvement and majorly complying to regulatory requirements.

Operational excellence also came with its own challenges. The challenges for a small scale pharmaceutical manufacturing industry were reviewed. The main challenges were for vendor management, process development and formulation development. Vendor management included vendor approval system. There is a challenge for any small scale industry to have a dedicated role for the same. This leads to approval of vendors on sample basis and not on site audits, many imported raw materials are skipped for site audit and hence partial vendor approval is achieved leading to hurdle in regulatory compliance. Many of the existing process were started long back and the processes have been upgraded for productivity but not reviewed with respect to its impurities. Thus, there is complete product knowledge but partial process knowledge which again leads to hurdle for regulatory compliance. Gaining complete process knowledge can also aid in ‘right at first time’ approach which leads to operational excellence [4].

### 1.2. Driving forces of operational excellence

On reviewing the impact and challenges of operational excellence, some driving forces were also found. These driving forces are the requirements for achieving this excellence. These driving forces include people involved in manufacturing and the process of manufacturing. The people and their mindset plays a major role in bringing the continual improvements in the organization. This mindset is generally top management driven. The process with respect to its raw material, equipment, utilities, etc also plays a major role in achieving operational excellence [9].

### 1.3. Enablers of operational excellence

All those tools which are used to achieve operational excellence were termed as enablers. These included total productive maintenance (TPM), total quality management (TQM), just – in -time, effective management system (EMS), kaizen, lean six sigma and pharma 4.0. These enablers were reviewed to understand their implementation in various process to achieve improvements. These enablers can be either used as a single tool or in combinations to achieve the required goal. Every enabler is also reviewed for its key performance indicator. This provides us a complete knowledge of concept of every enabler, their applications and their key performance indicator. This knowledge gained helps in designing a roadmap to achieve the required improvement in the organization. When the roadmap is well thought and designed it leads to a smoother path towards achieving the goals.

## 2. Operational excellence for higher regulatory compliance

Literature was further explored to obtain insight on development and validation of a roadmap to achieve operational excellence. This roadmap was then strategized for this research work.

### 2.1. Case studies

Various case studies of pharmaceutical or aligned manufacturing industries were reviewed for the problem they identified, the goal they targeted to achieve and the enablers they used alongwith the outcomes. Nine case studies were reviewed and it showed that all could achieve their targets with proper utilization of enablers either solely or in combination. The case studies gave an authentication of implementing operational excellence in many projects of pharmaceutical industries. These case studies give a practical understanding to the envisioned approach.

### 2.2. Development of assessment roadmap

Roadmap is the strategy designed by the company to achieve operational excellence. Every company first notes down their current state and the state they aim to reach. A complete gap analysis is done between these two states. To close the gap various projects are designed and they are listed and prioritised based on various factors like available resources and ease of implementation. The organization can schematize a roadmap based on the priorities of the projects. Every project can be allotted an enabler or combination of enabler. This can be accommodated with their key performance indicators and timelines. Together after every review

the strategy will lead to desired state of the organization. This will aid in achieving operational excellence.

**2.3. Validation of assessment roadmap**

The assessment roadmap schemed must be validated for its application. Literature was reviewed for the same. At the initial stage, it should be discussed with managers, supervisors, and operators. This provides the level of understanding and acceptance amongst the people. Validation of the roadmap is done allowing for some flexibility and timeline of the roadmap [10].

**2.4. QbD approach for synthesis of API**

Quality by design (QbD) is a concept that achieves the target profile of the product considering all factors which can influence its quality. Hence, it is one of the best approaches to obtain a robust method to synthesize a quality product. QbD approach requires us to study the selection of raw materials for targeting quality products. It disallows over usage of any utility or material which helps industries achieve operational excellence and ensure higher regulatory complianc [11]. QbD can be achieved using Design of Experiments (DoE) which leads to certain permutation and combination of variable factors hence we do not fall into a long list of experiments by changing one variable at a time. This results in an optimized process which aids in robust control strategy along with its process understanding which ensures quality of API [12]. Thus it highlights that an optimized process can lead to better manufacturing excellence and thus ensure regulatory compliance [13].

**3. Research envisaged and plan of work**

Implementing a framework of operational excellence leads the organization towards higher regulatory compliances. New synthetic approach from the view of operational excellence involves selections of raw material with required critical material attributes. Such quality by design produces final product without any quality variations and help achieve quality compliance. It can also reduce cost for the manufacturing of final product due to lesser rejections or reprocessing required. Development and optimization of process which is cost, time and process efficient will lead to operational excellence for the organization. The process optimized can be efficient to use less fuels and produce lesser environmental pollution. Such process will be regulatory compliant with respect to environment safety, health and occupational safety as well as quality safety.

The present study was designed to reflect implementation of QbD approach for synthesis of two different salts on operational excellence. The two salts in this study are ferric ammonium citrate and calcium orotate.

### 3.1. Objectives

The objectives of this research work were as follows:

- To study the impact of operational excellence on ensuring higher regulatory compliance
- To find newer synthetic approach for the synthesis of ferric ammonium citrate and calcium orotate respectively which is operationally excellent.
- To compare the newer approach with other synthetic process and evaluate the benefits.

The synthesis study on each salt is described briefly in further sections.

## 4. Synthesis of ferric ammonium citrate

Ferric ammonium citrate is selected as an iron salt for the study. It is a hematinic agent. The main rationale for selecting this drug is that it is available in various grades like I.P. / B.P. / U.S.P. and B.P.C. It also has a large market for manufacturing. The molecule is old and many small scale industries uses old manufacturing process. These industries will benefit by upgrading their processes to achieve higher regulatory compliance. The objective was to find new synthetic approach to manufacture ferric ammonium citrate compliant with specifications as per IP 2018 monograph. The developed method was optimized and scaled up. It was also compared with other process to evaluate the excellence of new synthesis. The stages of process development are described below:

### 4.1. Selection of key starting material

An exhaustive literature search was done to find possible key starting material for the molecule. This is critical step as the quality and type of key starting material impacts the quality of product and the excellence level of the process. It was reviewed that ammonia gas was less regulatory friendly compared to ammonium hydroxide. It was also reviewed that citric acid monohydrate was more economical and practical approach to be used as a key starting material when compared with citric acid anhydrous. Iron powder, ferric chloride and ferrous sulphate were three possible iron source key starting material. These are those key starting ingredients which direct the reaction mechanism and are also responsible for the iron supplementation nature of the

drug. It was reviewed that ferrous sulphate and ferric chloride provide by-products like sodium sulphate and sodium chloride respectively. These by-products needed to be washed out and treated for effluent. These two key starting material also required additional steps and in-process checks. Whereas, iron powder used a lesser step process with release of water as a by-product. Thus, the process with iron powder is more environment friendly and regulatory compliance friendly. As a result of the above review reaction mechanism with iron powder, citric acid monohydrate and ammonium hydroxide as key starting material were explored further.

### 4.2. Selection of oxidising agent

The process reviewed required a step of oxidizing ferrous ions to ferric ions. This oxidation could be carried out using various mechanisms. Oxidising agents like air, nitric acid, sulphuric acid, potassium permanganate and hydrogen peroxide were reviewed for its advantages and disadvantages. Air and nitric acid were considered strong and safe oxidising agents and hence shortlisted for conducting preliminary trails. Hydrogen peroxide and sulphuric acid were considered hazardous for use in a manufacturing unit. Hence, these were not taken ahead for trials. Potassium permanganate was ruled out owing to its strong color and nature. Thus, out of all reviewed oxidising agents, air and nitric acid were used during preliminary trails.

### 4.3. Preliminary trails

Based on the reaction mechanism shortlisted and oxidizing agents selected preliminary trails to synthesize ferric ammonium citrate were taken. Firstly citric acid was dissolved in distilled water. To this iron powder was slowly added with stirring, the slurry was then given oxidizing treatment. The slurry turned dark in color and a clear solution was obtained. To this solution, ammonium hydroxide was added to neutralise the ferric citrate solution giving ferric ammonium citrate. This neutralised solution was concentrated, filtered and dried to obtained the crude drug. Trials involved complete usage of air, complete usage of nitric acid and a combination use of nitric acid and air bubbling. The details are mentioned in table 1. It was observed that only air bubbling took 36 hrs and gave crude drug which was darker in shade than the required description. When only nitric acid was used as oxidizing agent, the process was 16 h but nitric acid released lot of fumes which makes the process non ecofriendly. The third preliminary trail was taken using a combination of air bubbling and nitric acid. This resulted in process which was completed in 20 h and released controlable amount of nitric acid fumes. Hence, this process was taken further for optimization.

Table 1: Details about preliminary trials for selection of oxidizing agent (Batch size 400 g)

| Batch No. | SC/PHD/FAC/P1 | SC/PHD/FAC/P2 | SC/PHD/FAC/P3 |
|---|---|---|---|
| Quantity of Iron powder | 90 g | 90 g | 90 g |
| Quantity of Citric acid monohydrate | 235 g | 235 g | 235 g |
| Quantity of aqueous ammonia | 218 g | 218 g | 218 g |
| Oxidizing agent used | Air bubbling | 50% v/v Nitric acid solution | Combination of air bubbling and 50% v/v nitric acid solution |
| Observation | The final product is blackish powder and does not comply with the description as per the IP monograph. | The final product complies as per the IP monograph concerning the description, solubility, and Fe content. | The final product complies with the IP monograph concerning the description, solubility, and Fe content. |
| Time required for the process | 36 h | 16 h | 20 h |

### 4.4. Optimization of process

The process was optimized to make it operationally excellent. QbD approach was used to optimize the process. For which firstly factors affecting the process were noted and evaluated for its impact on critical quality attributes. These factors were depicted as Ishikawa diagram (fish

bone diagram) as shown in figure 1. It was found that people, process, equipment and facilities, quality units and raw materials were the major factors affecting the quality of the product.

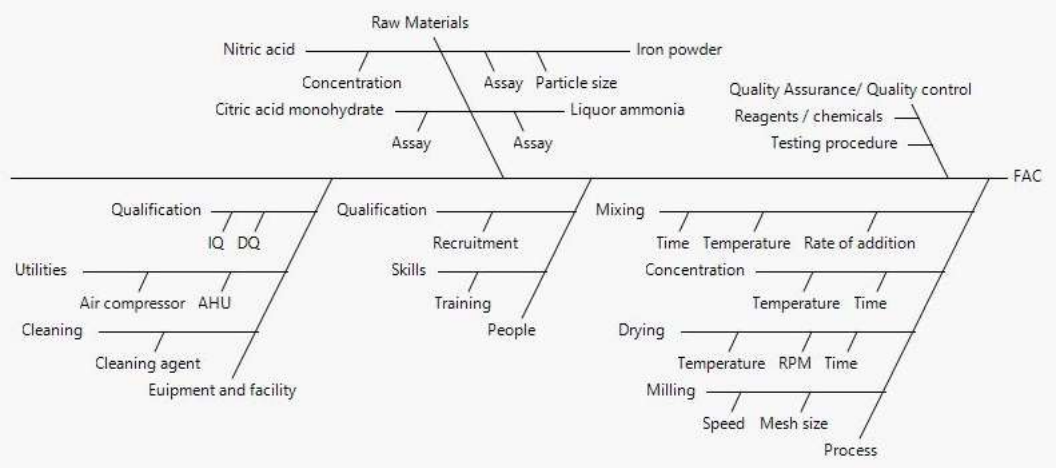



Figure 1: Ishikawa diagram for factors affecting the quality of FAC

Quality risk assessment was also performed using FMEA model for all the factors and their control strategies were also considered. The FMEA noted that raw materials and process were the most critical factors. The quantity of raw materials would remain as per reaction mechanism but their quality was controlled by using raw materials of approved specifications.

The process parameters which are variable factors were further optimized. DoE was used to optimize the time for air bubbling and quantity of nitric acid. Central composite design resulted in 10 runs of various combinations of air bubbling time and quantity of nitric acid. Trails for a batch size of 400 g were taken. The responses in the form of % yield, Fe content and description were recorded. The responses showed that all 10 experiments were capable of producing ferric ammonium citrate of desired quality. The recorded responses are mentioned in table 2.

Table 2: Responses obtained for every batch of Central composite design of experiments

| Sr. No. | Batch No. | Factors | | Responses | | |
|---|---|---|---|---|---|---|
| | | Level of 50% v/v nitric acid | Level of air bubbling | Description | % yield | Fe Content |
| 1 | SC/PHD/FAC/D01 | 140 g | 8 – 10 h | 2 | 20.9% | 22.1% |
| 2 | SC/PHD/FAC/D02 | 120 g | 12-15 h | 4 | 55.4% | 21.9% |
| 3 | SC/PHD/FAC/D03 | 130 g | 8 - 10 h | 3 | 24.1% | 21.8% |
| 4 | SC/PHD/FAC/D04 | 140 g | 12-15 h | 3 | 57.4% | 21.3% |
| 5 | SC/PHD/FAC/D05 | 130 g | 18 - 20 h | 5 | 82.3% | 20.9% |
| 6 | SC/PHD/FAC/D06 | 130 g | 12 - 15 h | 4 | 62.3% | 21.2% |
| 7 | SC/PHD/FAC/D07 | 140 g | 18 – 20 h | 3 | 74.3% | 21.9% |
| 8 | SC/PHD/FAC/D08 | 120 g | 8 – 10 h | 4 | 30.2% | 21.7% |
| 9 | SC/PHD/FAC/D09 | 120 g | 18 -20 h | 5 | 85.4% | 22.3% |
| 10 | SC/PHD/FAC/D10 | 130 g | 12– 15 h | 4 | 64.3% | 21.8% |

### 4.5. Graphical analysis

The responses recorded were graphically analysed using 3D response graphs and contour plots. Prediction profiler was also used to confirm the optimized values of air bubbling time and quantity of nitric acid. 3D response surface graphs showed in figure 2. It highlighted that % yield increases with an increase in air bubbling time and there is not much difference with an increase in nitric acid content. It also shows that description value increases with an increase in air bubbling time but decreases with higher nitric acid content. 3D response plots also showed that Fe content does not indicate any specific relation.

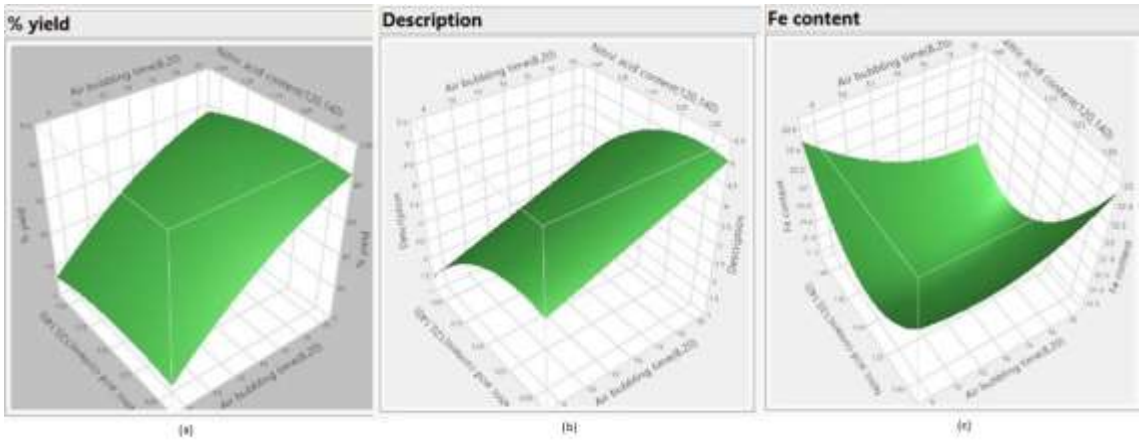



Figure 2: (a) 3D response surface plot for % yield, (b) 3D response surface plot for description, (c) 3D response surface plot for Fe content

Contour plots as shown in figure 3 were also recorded to find the optimized values. It showed that % yield was highest when the air bubbling time was between 19- 20 h and nitric acid content was 120 -132 g. It also indicated that Fe content was in the preferable range (21.8 - 22.5) when the air bubbling time was 16 – 20 h and the nitric acid content was 120 – 125 g. Contour plot for the description of the product showed that when air bubbling time is 15 – 20 h and nitric acid content is 120 – 135g the description is best achieved.

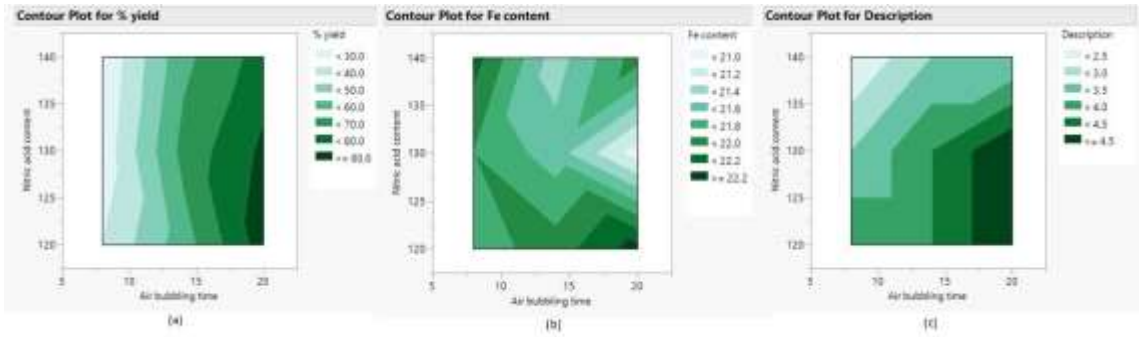



Figure 3: (a) contour plot for % yield, (b) contour plot for Fe Content, (c) contour plot for description

These contour plots of three different responses were overlayed as shown in figure 4. It highlighted that Fe content of more than 21.5 with a description value between 4- 5 and the

highest % yield can be achieved when the air bubbling time is 18.9 h and nitric acid content is 125.3 g.

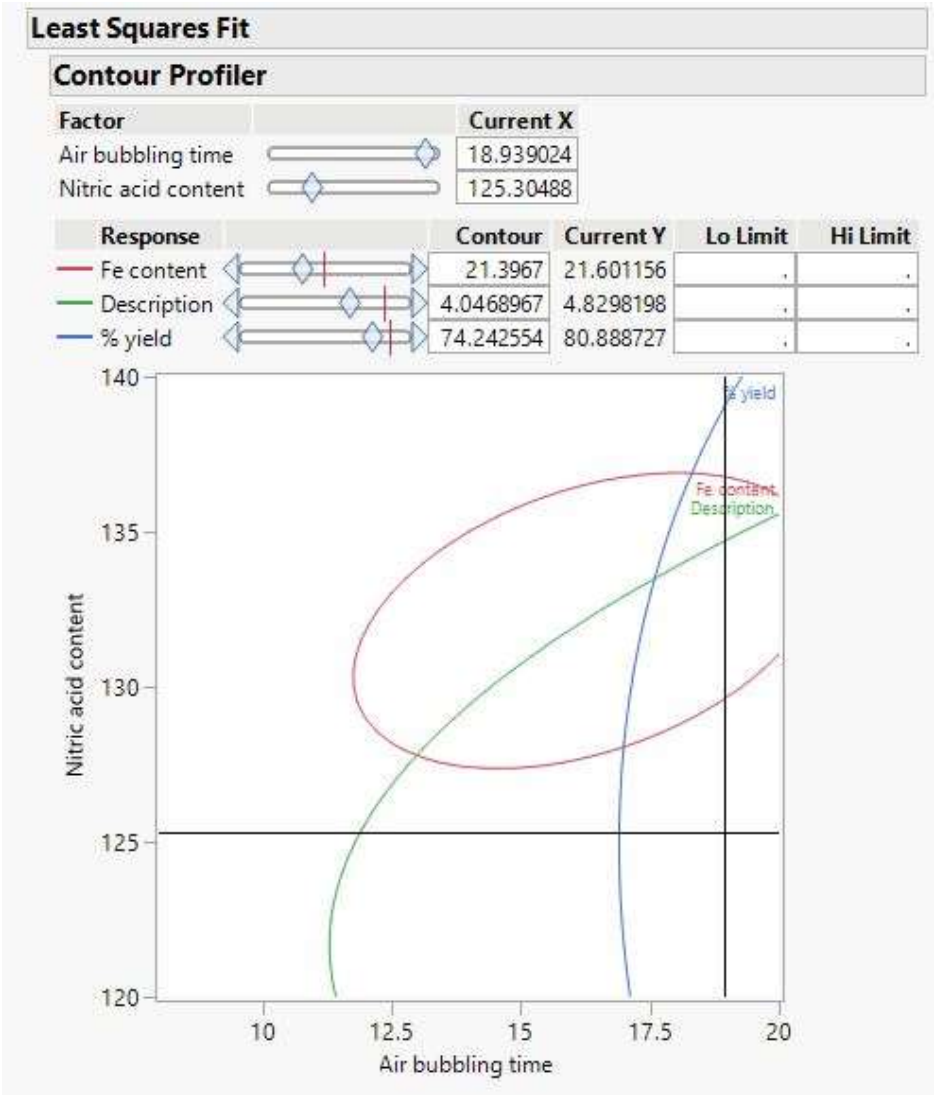



Figure 4: Overlay of contour plots for Fe content, description and % yield against air bubbling time and nitric acid content

The prediction profiler as shown in figure 5 was also used to further confirm the optimized values. It showed that desirability value which was preferred to be close to 1 can be achieved with optimized values of 18.6 h of air bubbling and 126 g of nitric acid.

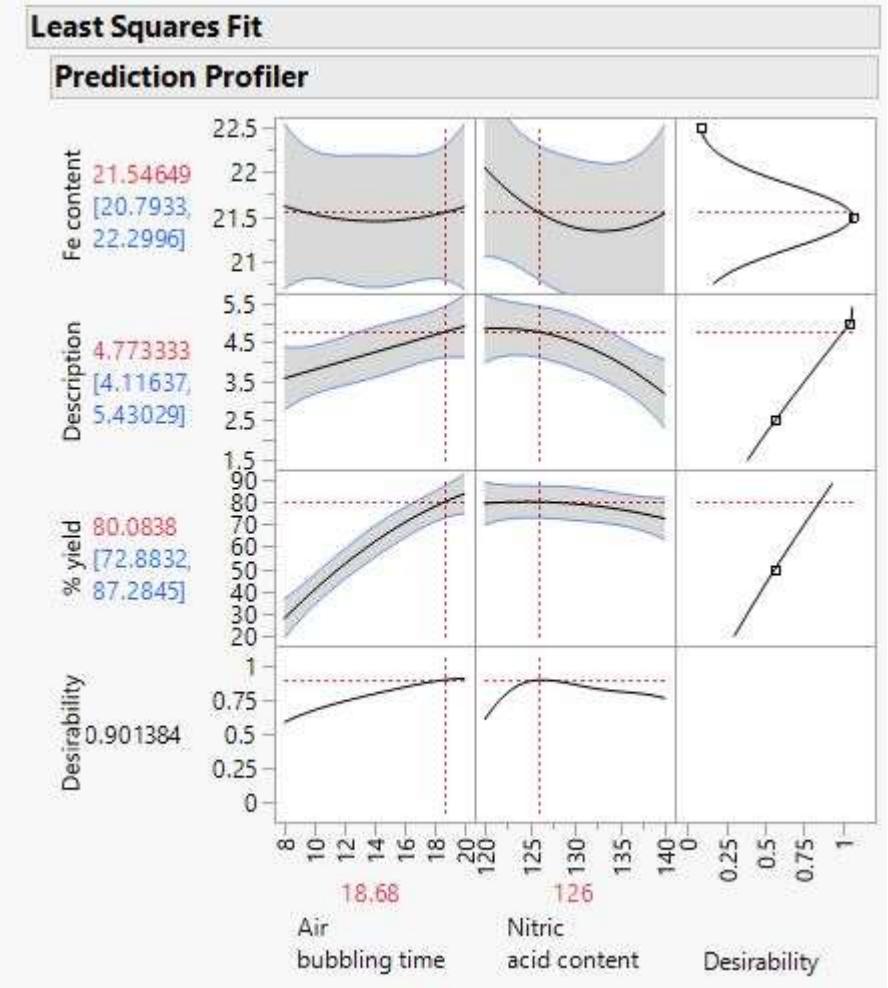



Figure 5: Prediction profiler for the optimization of variable factors

Considering all the graphical representations and prediction profilers, the value of air bubbling time should be 19 h and the content of nitric acid must be 125 g for the batch size of 400 g of Ferric ammonium citrate. Another batch with optimized process was synthesized and characterised with respect to its complete testing as per IP monograph. It was also characterized using UV spectroscopy, NMR spectrum, FTIR spectrum and XRD spectrum. The synthesised ferric ammonium citrate was of required quality.

### 4.6. Repeatability and scale up of batches

Using the optimized process batches were repeated in triplicates (batch size 400 g). This assured the repeatability parameter as part of validation. All three batches were tested as per complete IP specifications and found to compliant. Another batches (Batch size 4 kgs) were also synthesized in triplicates as scale up batch (10x). These batches were also tested as per complete IP

specifications and found to be compliant. The laboratory scale batch and scale up batch were synthesized practically and commercial batch (100x) was discussed with the industrial expert for the changes to be made in manufacturing process. These comparison of various batch sizes are described in table 3.

Table 3: Equipment and process parameter for lab, pilot and commercial scale batches

| Equipment/ process | Lab scale | Pilot scale | Commercial scale |
|---|---|---|---|
| Batch size | 400 gms | 4 kgs | 4000 kgs |
| Reaction vessel | Stainless steel vessel with homogenizer | Stainless steel vessel with homogenizer | Stainless steel reactor with stirrer |
| Filteration unit | Vacuum filteration using buckhner funnel | Vacuum filteration using buckhner funnel | Filter press |
| Dryer | Tray drying using hot air oven | Tray drying using hot air oven | Drum dryer |
| Milling | Grinder (single batch) | Grinder (multiple batch) | Multimill (multiple batch) |
| Blending | Not required | Mixing pan (manually) | Octagonal blender |
| Air bubbling time | 19 h | 19 h | 19 h |
| Amount of conc. Nitric acid | 125 gms | 1.25 kgs | 1250 kgs |
| RPM of stirrer | 60 RPM | 60 RPM | 60 RPM |

### 4.7. Comparison with other possible processes

The optimized process was compared with other possible processes of manufacturing to evaluate its excellency. The other processes considered were using ferric chloride and ferrous sulphate as key starting material respectively. It was found that raw material cost of current process was higher compared to other processes. It was also evaluated that the cost for additional steps like washing required more manpower and time and hence not considered to be efficient process. The disposal of effluent of other processes also enquired certain cost. It was concluded that, the process using iron powder was overall more cost effective and operationally excellent.

## 5. Synthesis of calcium orotate

This research work had a calcium salt also under its scope. Various calcium salts available for use as a calcium supplement were reviewed and calcium orotate was selected further for study. This calcium salt is not available in any pharmacopoeia and hence, initially its specifications were developed. The methods globally available were adapted but the method for estimation of orotic acid form calcium oroate which was not available in literature was developed and validated. The synthesis of this calcium orotate was explored by preliminary trials using two different key starting material and two different method of preparation. The selected process was then optimized and the batch was repeated and scaled up. This process was also theoretically compared with other possible processes for its excellence. The summary of all the work done for calcium orotate is described below:

### 5.1. Selection of calcium salt

An exhaustive literature review on various calcium salts was conducted with respect to its chemical nature, manufacturing ease, mechanism of absorption and its key features were compared. Calcium carbinate, calcium citrate, calcium citrate malate, calcium acetate, calcium orotate, calcium aspartate, calcium gluconate, calcium ascorbate, calcium lactate were mainly compared. Out of all, it was reviewed that the carboxyl acid content plays a major role in determining the dissociation property of calcium salt to release calcium ions for absorption. Salts like calcium carbonate are also dependant on gastric pH for its dissociation. Calcium orotate was reviewed to be highly bioavailable and least dependant on external factors. But it was also reviewed that the orotic acid component plays a major role for its advantages. Owing to high bioavailability and high market demand calcium orotate was considered further for the research work.

### 5.2. Preparation of specification of calcium orotate

The selected calcium orotate salt is not available in any pharmacopoeia. Hence, it did not have any standard specifications for its quality target profile. As a result, we developed specifications globally acceptable based on ICH Q6 guidelines. The specifications evaluated all the required physicochemical and chemical properties for the quality of calcium orotate. It included description, solubility, identification by chemical reaction as well as instrumental identification, Loss on drying, limits for heavy metals, limits for sulphates, sieve test, pH of solution, complete assay of drug, separate calcium content, orotic acid content. These together was justified to have a quality calcium orotate for use as solid oral dosage supplements. The method for each test

parameter was explored in literature and they were accepted based on pharmacopoeial methods. It was found that no method was available for estimating only orotic acid content from calcium orotate. This was an important parameter as orotic acid ions play role in dissociation of calcium ions and thus affect its bioavailability. Thus, method for determination of orotic acid was developed and validated.

### 5.3. Method development for estimation of orotic acid content in calcium orotate

Literature was reviewed to develop an RP-HPLC method. It was reviewed to conduct trials using RP-HPLC with UV detector and C18 (ODS, 250 × 4.6 mm) column. The method was developed using water as dilutent and separation of orotic acid and calcium was achieved using 20mM of monobasic potassium phosphate in water adjusting the pH to 2.5 with phosphoric acid as a mobile phase with flow rate of 1.0 mL/min and injection volume of 20 µL at ambient temperature conditions. UV detector at 214 nm was used for detecting the peak of orotic acid. The method was validated and showed a linear response over the entire working range (12 µg/mL -28 µg/mL) with a correlation coefficient (r2) value of 0.9992. A typical chromatogram from this method is shown in figure 6. This method can be applied for regular analysis of calcium orotate bulk samples to assure its quality.

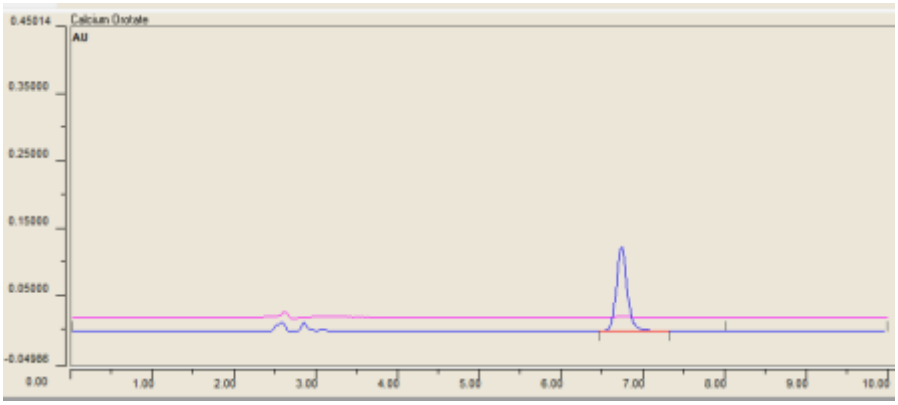



Figure 6: Overlay of the chromatogram of blank and standard orotic acid solution

### 5.4. Preliminary trials

For synthesis of calcium orotate literature was reviewed to shortlist key starting materials and design the preliminary trials. It was reviewed that, calcium hydroxide and calcium carbonate can be two potential key starting material for imparting calcium ions. It was also reviewed that, orotic acid monohydrate was the only relevant source of orotic acid ions. Thus two types of key starting material for calcium were designed into preliminary trials. It was also reviewed that

there could be two possible method of preparation at different temperature conditions. These were also considered in designing preliminary trials. The trial batches were evaluated for its % yield, assay and calcium content. The recorded results are shown in table 4.

Table 4: Results from preliminary trials for synthesis of calcium orotate (batch size 400 gms)

| Sr. No. | Batch No. | Method of synthesis | Orotic acid amount | Calcium hydroxide | Calcium carbonate | % yield | Assay | Calcium content |
|---|---|---|---|---|---|---|---|---|
| 1 | SC/PHD/CO/P 1 | Hot method | 50 gms | 11 gms | Nil | 80.52 % | 100.32 % | 10.41% |
| 2 | SC/PHD/CO/P 2 | Cold method | 50 gms | 11gms | Nil | 83.98 % | 104.6% | 10.92% |
| 3 | SC/PHD/CO/P 3 | Hot method | 50 gms | Nil | 14.8 gms | 81.22 % | 102.36 % | 10.35% |
| 4 | SC/PHD/CO/P 4 | Cold method | 50 gms | Nil | 14.8 gms | 82.12 % | 103.54 % | 10.54% |

From all the trials it was observed that % yield, assay and calcium content were satisfactory and hence all process delivered the required calcium orotate. It was also observed that trials using calcium carbonate liberated carbon dioxide which needed to be controlled. The trials using calcium hydroxide released water molecule as by product and hence made it environment friendly. Similarly, it was observed that when temperature conditions were increased to 60 ℃ the synthesized crude drug was sticky as compared to the synthesis at ambient temperature. Thus, it was concluded that calcium hydroxide and orotic acid monohydrate when processed at ambient temperature synthesizes calcium orotate of desired quality.

### 5.5. Optimization of process

From the preliminary trials, the process using calcium hydroxide and orotic acid monohydrate at ambient temperature conditions was optimized to achieve operationally excellent process. As an initial step, the factors affecting the process were noted. They are depicted as Ishikawa diagram as shown in figure 7.

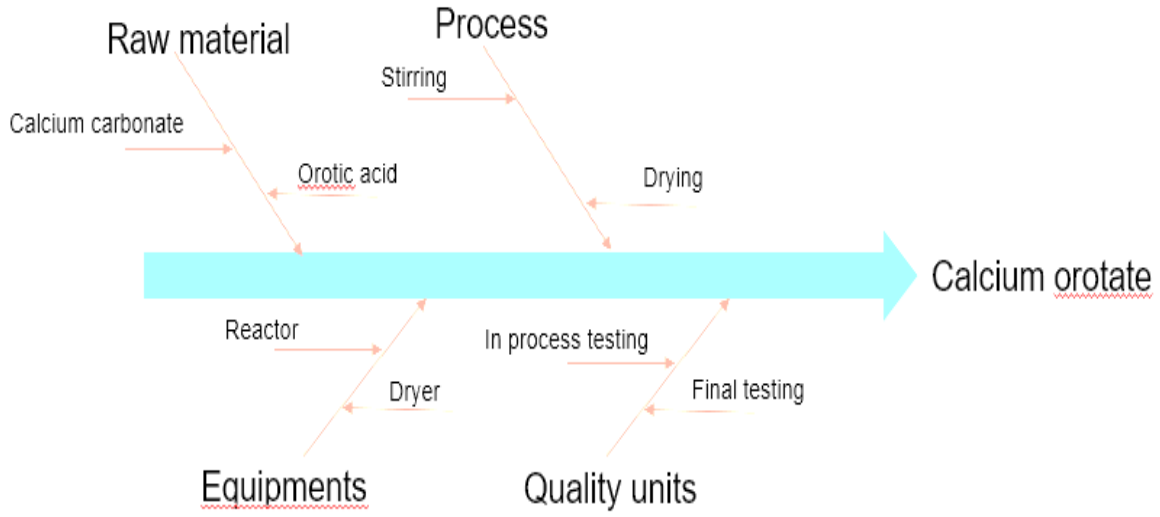



Figure 7: Factors affecting the process for synthesis of calcium orotate

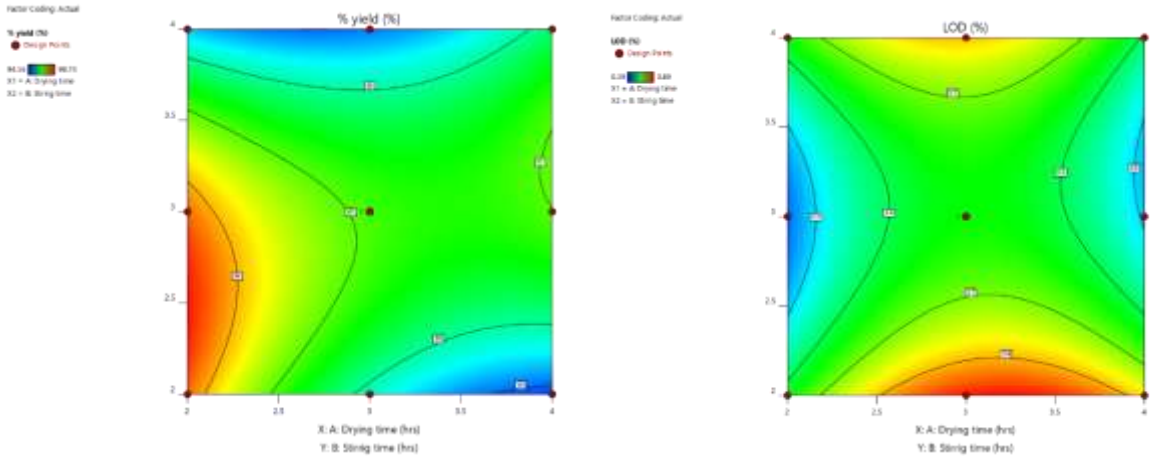
These were assessed for its risk factors and control strategies. Raw materials, process, equipment and quality units were considered to be major factors affecting the process. From the risk assessment using FMEA model. It was found that process was the most critical factor affecting the process and hence it was explored in details for optimization. The drying time and stirring time of the process was selected as critical parameter for optimization. Central composite design was used to design various combinations of drying time and stirring time. Drying time and stirring time of three levels of 2 h, 3 h and 4 h each were taken and responses for % yield, % LOD, assay, calcium content and orotic acid content were recorded. 13 experiments were designed and their responses were recorded as shown in table 5. It was observed that all resulted in products complying with required calcium orotate. It was also observed that low % LOD was obtained with drying time of 3 h and it had no co-relation with stirring time. Statistically there was no other co-relation observed.

Table 5: description of experiments and their responses

| Run# | Drying time (hrs) | Stirring time (hrs) | % yield | LOD(%) | Ca. content (%) | Orotic acid content (%) | Assay (%) |
|---|---|---|---|---|---|---|---|
| 1 | 3 | 3 | 97.81 | 0.79 | 10.65 | 89.56 | 102.66 |
| 2 | 4 | 3 | 96.53 | 0.39 | 9.68 | 90.65 | 100.98 |
| 3 | 3 | 3 | 98.21 | 0.43 | 10.93 | 90.25 | 99.65 |
| 4 | 2 | 4 | 94.58 | 0.63 | 10.51 | 90.66 | 99.87 |
| 5 | 2 | 3 | 98.61 | 0.51 | 10.4 | 90.23 | 98.94 |
| 6 | 3 | 3 | 95.33 | 0.81 | 10.09 | 89.62 | 100.52 |
| 7 | 3 | 4 | 96.21 | 0.74 | 10.26 | 89.54 | 101.36 |
| 8 | 3 | 2 | 94.56 | 0.89 | 10.46 | 89.36 | 100.12 |
| 9 | 4 | 2 | 95.66 | 0.81 | 10.76 | 90.52 | 99.52 |
| 10 | 2 | 2 | 98.74 | 0.58 | 9.84 | 89.74 | 100.23 |
| 11 | 4 | 4 | 95.84 | 0.66 | 10.03 | 88.98 | 102.52 |
| 12 | 3 | 3 | 96.52 | 0.46 | 10.39 | 89.52 | 101.63 |
| 13 | 3 | 3 | 96.82 | 0.76 | 10.46 | 90.52 | 101.54 |

**5.6. Graphical analysis**

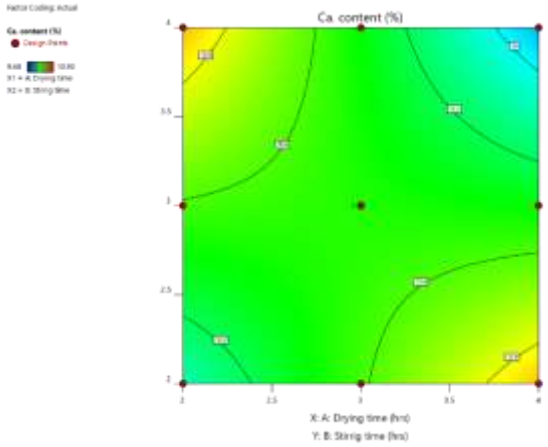
The responses recorded on design of experiments were also analysed graphically using contour plots, 3D response surface plots and prediction profiler. Contour plots are shown in figure 8 and it indicated that % yield can be maximised at 2 h of drying time and 3 h of stirring time. Whereas, minimum LOD can be obtained at 2 h of drying time and 2.5 h to 3.5 h of stirring time. Calcium content was in desired range when both drying time and stirring time were in the range of 2 h to 3.5 h. Orotic acid content was in the desired range when drying time and stirring time were in the range of 2 h to 3 h. It was also observed that assay was optimum at drying time and stirring time of 3 h each.



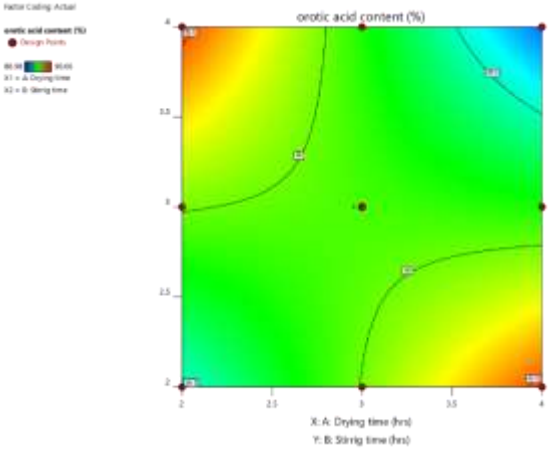

(a)



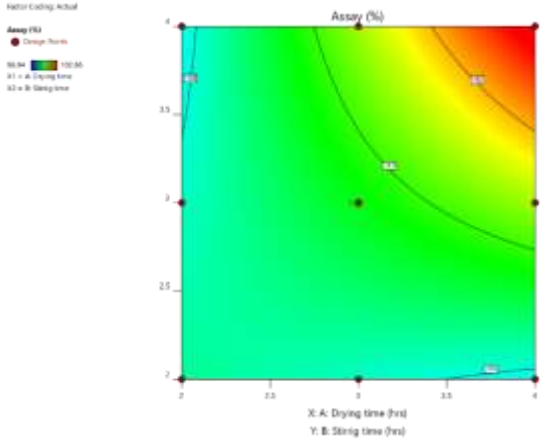

(b)




(c)



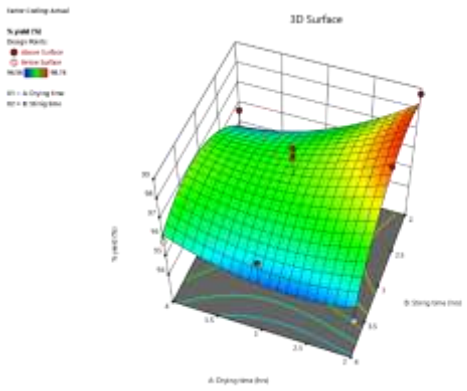

(d)



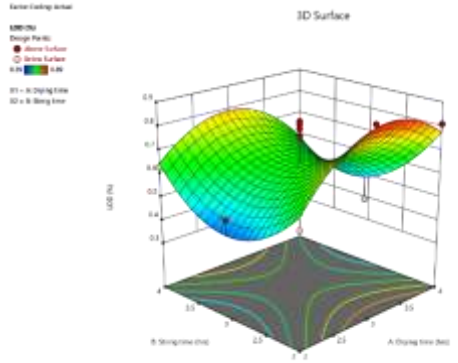

(e)

Figure 8: (a) Contour plot for % yield (b) Contour plot for % LOD (c) Contour plot for calcium content (d) Contour plot for orotic acid content (e) Contour plot for assay

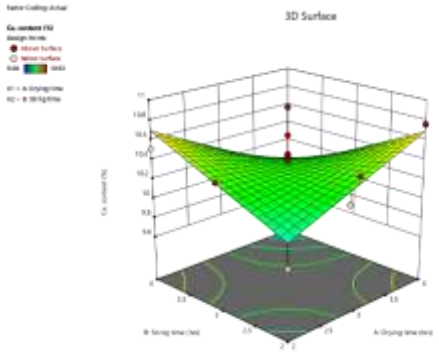
These results were verified using 3D response surface plots which mainly showed relation between the variables and the response. They are depicted in figure 9. It highlighted that % yield is inversely proportional to drying time whereas % LOD is directly proportional to drying time. It also shows all the levels of variables produces required assay, calcium content and orotic acid content.



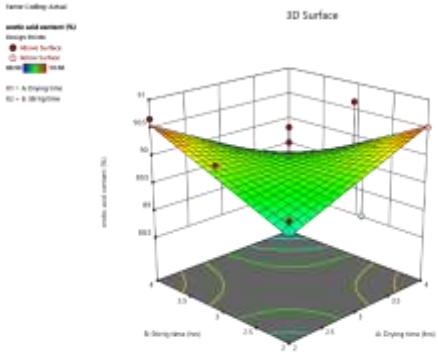

(a)



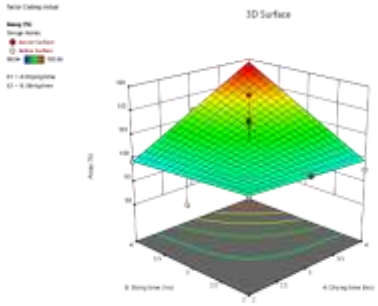

(b)




(c)




(d)




(e)

Figure 9: (a) 3D response surface plot for % yield (b) 3D response surface plot for % LOD (c) 3D response surface plot for calcium content (d) 3D response surface plot for orotic acid content (e) 3D response surface plot for assay

As part of graphical analysis further prediction profiler was used to find optimized values of variable parameters. The prediction profiler is shown in figure 10. It indicates that the desirability value of 0.912 showed drying time of 2h and stirring time of 3 h was optimum for the process for synthesis of calcium orotate.

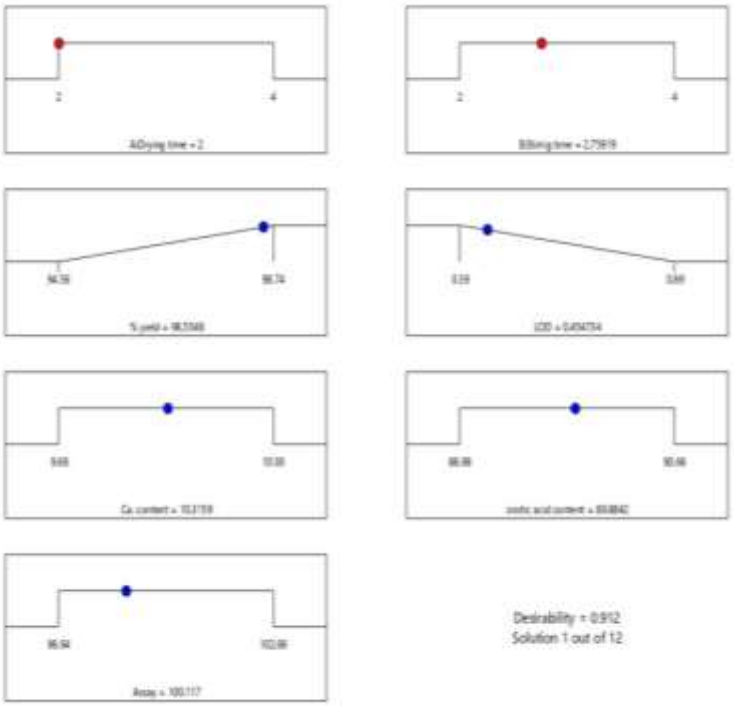



Figure 10: Prediction profiler for optimization of process parameter

Another batch was synthesized with the optimum values of process parameters. This batch was completely tested as per the specifications built and was characterized using UV spectrum, FTIR spectrum, NMR spectrum.

### 5.7. Repeatability and scale -up studies

The optimized batch was repeated in triplicates (batch size 400 gms) for assuring the repeatability parameter of validation. These batches were analysed for its complete specifications which were developed in house. The results showed that all batches complied to desired acceptance criteria. Scale up of these batches was also taken upto 10x (batch size 4 kgs). There was no major change of equipment or process. The scale up batch in triplicates delivered calcium orotate of desired specifications. Thus, the optimized process was repeatable as well as scalable. Discussions were done with the industrial expert as shown in table 6 comparing the practically synthesized laboratory and scale up batch (10x).

Table 6: Comparison of laboratory, scale up and commercial batch for calcium orotate

| Equipment/ process | Lab scale (x) | Pilot scale (10x) |
|---|---|---|
| Batch size | 400 gms | 4 kgs |
| Drying time | 2 h | 2 h |
| Stirring time | 3 h | 3 h |
| Reaction vessel | Stainless steel vessel with homogenizer | Stainless steel vessel with homogenizer |
| Filteration unit | Vacuum filteration using buckhner funnel | Vacuum filteration using buckhner funnel |
| Dryer | Tray drying using hot air oven | Tray drying using hot air oven |
| Milling | Grinder (single batch) | Grinder (multiple batch) |
| Blending | Not required | Mixing pan (manually) |
| RPM of stirrer | 8 RPM | 8 RPM |

### 5.8. Comparison with other possible processes

As part of the research to have an operationally excellent process, the optimized process was compared with other possible processes. These other processes included usage of calcium carbonate as key starting material. Raw material and disposal of waste were evaluated to statistically compare the cost difference between both the processes as rest process parameter were common for both due to same method of preparation. Calcium hydroxide is more expensive than calcium carbonate but if calcium carbonate is used then there is cost involved in air scrubber systems to manage the air pollution. Thus, a greener chemistry approach is operationally excellent from compliance point of view.

## 6. Conclusion

The entire research work drives through the importance and implementation of operational excellence for manufacturing of API. Out of various strategies to achieve operational excellence we practically achieved it for two different salts namely ferric ammonium citrate and calcium orotate. QbD approach was used to synthesize these API with an optimized process which is economic as well as environment friendly. Thus, QbD approaches for synthesis of conventional or newer molecules can aid in achieving operational excellence for

the company. This can eventually lead to continual improvement and thus higher growth of the organization.

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## 8. Publications and presentations

### 8.1 Publications

- Jalundhwala, F. and Londhe, V. (2022), "A systematic review on implementing operational excellence as a strategy to ensure regulatory compliance: a roadmap for Indian pharmaceutical industry", *International Journal of Lean Six Sigma*, Vol. ahead-of-print No. ahead-of-print. https://doi.org/10.1108/IJLSS-04-2022-0078. (Impact factor – 5.686)
- Jalundhwala, F., Londhe, V. & Shah, B. "Ensuring regulatory compliance by quality by design (QbD) approach to optimize the manufacturing process of API: ferric ammonium citrate as an example." *Chemical Papers*. (2022). https://doi.org/10.1007/s11696-022-02569-3. (Impact factor – 2.146)

- Entitled 'Estimation of orotic acid content from bulk calcium orotate' is communicated to journal of Iranian chemical society.
- Entitled 'Design and optimization of eco-friendly one-pot synthesis of Calcium orotate using Quality by Design approach ' is ready for communication

### 8.2. Presentations

- Abstract titled 'Impact of key starting material on regulatory compliance: an evaluation of ferric ammonium citrate' was presented as oral presentation at 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences, Abu Dhabi, UAE.
- Abstract titled 'Operational Excellence - Achieving quality compliance for a small scale manufacturing industry' was presented as oral presentation at 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences, Glasgow, Scotland.
- E –poster titled 'Estimation of orotic acid content in calcium orotate salt using

reversed phase HPLC method' was presented at virtual poster showcase organised at IPA Annual Convention2021

- Poster entitled 'Understanding the knowledge skills and attitude of pharmacists towards oral calcium supplements' was presented at FIP Summer Meeting 2022, Utrecht, The Netherlands

**8.3. Grants and scholarships**

- FIP Travel Scholarship Award for attending 78th FIP World Congress, 2018, Glasgow, Scotland, 2018.
- CSIR travel grant for attending 80th FIP World Congress, Seville, Spain, 2022. (Awarded but not availed)

**Candidate** **Supervisor**

**Forum J. Jalundhwala** **Dr. Vaishali Y. Londhe**